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Progress report: Pittsburgh Breast Cancer Consortium:

Principal Investigator: Adam Brufsky, MD, PhD

The University of Pittsburgh Cancer Institute, the Magee-Women's Hospital, the Hematology-Oncology Associates of the UPCI (HOA), the Pittsburgh Clinical Research Network, Inc. (PCRN), the Magee Womancare Breast Cancer Volunteer Program, and the Pittsburgh Branch of the National Association for the Advancement of Colored People (NAACP) are collaborating to form the Pittsburgh Breast Cancer Consortium (PBCC). The focus of this partnership is the rapid clinical development of new agents for the treatment of metastatic breast cancer (MBC). The PBCC will conduct innovative phase I and phase II clinical trials testing new approaches in the treatment of MBC. Accrual to these trials will derive from a consortium of Pittsburgh regional, community based oncology practices of the HOA in collaboration with the Magee-Women's Hospital/University of Pittsburgh Cancer Institute Comprehensive Breast Cancer Center (CBCC). The Consortium will be centered at the University of Pittsburgh Cancer Institute (UPCI), an NCI-designated Comprehensive Cancer Center. The UPCI, which has an outstanding clinical trials support infrastructure, will provide the template for development of central data management, coordination oversight, trials auditing, biostatistical support, pharmacokinetic analysis, and interaction with industrial partners. The PBCC will establish the mechanisms for the conduct of new studies, with a strong emphasis on community-based practice involvement. In addition, the PBCC will be overseen and advised by a central governing board for the Consortium, meeting monthly, composed of representatives of the UPCI, the HOA, the PCRN, the volunteer group, and the NAACP.

The specific aims of this proposal are (1) to develop a breast cancer clinical trials infrastructure to allow the rapid phase I and phase II development of novel agents for the treatment of breast cancer with a strong emphasis on community-based practice involvement; and (2) to evaluate multiple agents, as well as combinations of agents, using this infrastructure.

In this progress report, we will detail how our objectives to date have been met. The workstatement will be used as a template. To briefly summarize, we have established the infrastructure of the PBCC and are currently conducting clinical trials of novel agents and combinations of agents. As noted in the original proposal, priorities of industrial sponsors change, as do the availability of agents. While we have not conducted all of the proposed clinical trials, other trials have been and are currently being conducted in the PBCC.

Statement of Work:

Task 1: Develop the PBCC Infrastructure (Months 1-12)

- Recruit and train nurse-coordinators. This has been done. Our governing committee decided that the best method of increasing community nurse coordinator support of PBCC clinical trials would be to buy time from existing community coordinators. The PBCC now pays for three full time coordinators at the central site at Magee-Women's

Hospital as well a 2/9 FTE of each of nine community coordinators. Each of the coordinators is expected to accrue 9-12 patients per year onto PBCC clinical trials to continue receiving support.

- Recruit and train data managers. This has been done. There are currently two data managers supported by the PBCC working at Magee-Women's Hospital.
- Educate community oncologists about the PBCC. This is currently underway. Dr. Brufsky meets quarterly with small groups (6-10) community oncologists to discuss PBCC trials and accrual goals. In May 2003, prior to the Koman Race for the Cure in Pittsburgh, a marketing company retained by the PBCC (Jack Horner Communications) will announce our consortium to the lay public of Pittsburgh. A brochure describing the PBCC with a logo specific to the PBCC has been created. Physicians participating in the PBCC will receive wall plaques to be displayed in their offices announcing their participation. The PBCC has also retained a web design company (GIST) to build and maintain a PBCC web site for physicians and lay public. The content of this website is under review by our IRB and is scheduled to be uploaded to the site by March 2003.
- Initiate PBCC governing board and set schedule of meetings. This has been done, but we have currently scheduled meetings bimonthly. Due to various migrations of faculty members, the current composition of the board is Adam Brufsky, MD, PhD; Merrill Egorin, MD; Ron Herberman, MD; Lyn Robertson, MSN; Barry Lembersky, MD; Sam Jacobs, MD; Victor Vogel, MD; and representing the patients, Kathy Purcell, MSW. We intend to add Anne Humphires as a patient representative by the next meeting, after using her extensively as an informal consultant.
- Initiate protocol processing through the PCRN and IRB. This has been done. Two trials from the Lilly Corporation have been initiated through PCRN solely, and at least six trials for MBC have been initiated in total since the start of funding.
- Test existing UPCI-Based Intranet and PCRN protocol. Web server and develop PBCC Web site. See above. GIST corporation has taken the lead in developing the PBCC Web site (which went active in September 2002) and we are currently constructing the protocol Web server.

Task 2: Evaluation of Novel Compounds for the Treatment of Metastatic Breast Cancer (MBC) in the PBCC (Months 1-36) (As noted above, certain protocols were not intiated and were replaced during the first 18 months of this award)

- Phase I trial of 17-AAG (anti-HSP 90). This trial was completed, and results will be presented at ASCO 2003.
- Phase II trial of L-778,123 (farnesyltransferase inhibitor) in MBC. This trial was completed, and we are currently analyzing the data.
- Phase II trial of oral dexamethasone and calcitriol in MBC. Due to the departure of Dr. Trump from the UPCI, this trial is currently on hold.
- Phase II trial of MUC-1 peptide vaccination in women with MBC. This trial is currently in development with Dr. Olga Finn and Dr. Joseph Baar, and will likely open in the 4th Quarter of 2003.

- Phase II trial of traztuzumab and tamoxifen in tamoxifen-resistant MBC. This trial is on hold by the sponsor (Genentech).

Other current trials performed by the PBCC:

- Phase II trial of Carboplatin/taxotere in MBC (Aventis). This trial was added to the PBCC in October 2000, and accrual thereafter was rapid. This trial was completed in December 2001, and we are currently analyzing the data and preparing a manuscript for publication.
- Phase II trial of Carboplatin/taxotere/Herceptin in MBC (Aventis). This trial was added to the PBCC in October 2000, and accrual thereafter was also rapid. This trial was completed in September 2002, and will be presented at ASCO 2003. We are currently analyzing the data and preparing a manuscript for publication.
- A phase II, Multicenter, Randomized, Open-Label, Dose Comparison Study of Recombinant Human Chorionic Gonadotropin for Third Line Treatment of Metastatic Breast Cancer in Postmenopausal Women (Ares-Serono). We accrued 12 patients in the PBCC (12% of total) in this Multicenter trial. The trial is complete, and the data is currently being analyzed for presentation.
- A multicenter, open-label, phase III, randomized, active-controlled trial evaluating the efficacy, safety, and pharmacokintics of rhuMAb VEGF, in combination with capecitabine chemotherapy, in subjects with previously treated metastatic breast cancer (Genentech). The PBCC accrued 10 patients on this Multicenter phase II study. This trial is currently complete.
- Phase II trial of Gemcitabine/Herceptin in MBC (Lilly). This multicenter trial was brought to the PBCC by the PCRN in March 2002. This trial is currently underway, with the PBCC responsible for 8 of the 17 accruals nationally.

The PBCC plans on several trials to open in the next 1-2 months specific to refractory MBC. These include:

1. A phase II trial of an epothilone (NCI);
2. A phase II trial of a novel taxane (Aventis) that crosses the blood brain barrier;
3. A phase II trial of a novel oral inhibitor of the tyrosine kinase associated with Her2 Neu;
4. A phase II trial of a novel Her2 Neu peptide vaccine;
5. A phase II trial to individually characterize chemoresistance in women with MBC, using a novel chemosensitivity assay and cDNA expression profiling (Precision Therapeutics, Incorporated).

Task 3: Dissemination of Research Results (Months 18-36)

- Presentation of PBCC infrastructure results to USAMRMC-BCRP Symposium (Month 24). Dr. Brufsky will attend the DOD meeting in September 2003 to present results.
- Preparation and publication of results from clinical studies from months 1-24 (Months 24-36). This is currently underway as noted above.

- Visits to the PBCC for industry representatives, faculty, and community physicians (Months 18-36). This is also currently underway as noted above.